



Risk Evaluation and Mitigation Strategies (REMS)

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Objectives

- To provide general information regarding Risk Evaluation and Mitigation Strategies (REMS), including:
 - brief information regarding the Food and Drug Administration Amendments Act (FDAAA) of 2007
 - FDA authorities under FDAAA, Title IX, Subtitle A, section 901
 - RiskMAPs and REMS
 - Possible elements to REMS
- To identify resources on the FDA website for information regarding REMS

What is FDAAA?

- Food and Drug Administration Amendments Act of 2007*
- The President signed into law, FDAAA, on Sept. 27, 2007 before certain existing laws were set to expire on September 30, 2007
- FDAAA is the name for legislation that adds many new provisions to the FD&C Act to provide important resources and strength to the agency's ability and commitment to safeguard and advance public health

*<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm>

Food and Drug Administration Amendments Act (FDAAA) of 2007

- New Safety Authorities under FDAAA Title IX –
 - Require postmarketing studies and clinical trials
 - Require sponsors to make safety related labeling changes
 - Require sponsors to develop and comply with risk evaluation and mitigation strategies (REMS)
- New authorities effective 180 days after enactment of FDAAA, March 25, 2008
- This talk will focus on REMS

*<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FoodandDrugAdministrationAmendmentsActof2007/ucm095438.htm>



Risk Management Before FDAAA

- Most basic risk management tool was, and still is, the labeling directed to prescribers
 - Labeling contains directions for use, warnings, precautions, contraindications, and underlying data on efficacy and safety
- In some cases, the labeling might include a Medication Guide or Patient Package Insert with information directed to patients
- When a drug posed more significant risks, a risk management plan might be agreed upon; plans included a range of risk management tools from education to restricted distribution of the drug
- 16 drugs were approved with restrictive risk management programs before FDAAA (e.g., isotretinoin, thalidomide)

Risk Management Pre-FDAAA RiskMAPs

- Before FDAAA, a small number of drug and biological products were approved with risk minimization action plans (RiskMAPs).
- A RiskMAP was a strategic safety program
 - designed to meet specific goals and objectives to minimize known risks while preserving its benefits
 - developed for products that had risks that required risk management strategies beyond the required labeling and safety reporting.
- In 2005, FDA issued a Guidance for Industry on *Development and Use of Risk Minimization Action Plans** describing how to
 - develop RiskMAPs
 - select tools to minimize risks
 - evaluate and monitor RiskMAPs and monitoring tools
 - communicate with FDA about RiskMAP.

* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf>



FDAAA Clarified FDA's Authority

- FDAAA clarified FDA's authority to require enforceable risk management programs (REMS)
- The REMS provisions of FDAAA were built on previous experience with risk management plans (RiskMAPs) and the Guidance for Industry: Development and Use of Risk Minimization Action Plans (March, 2005)



REMS

- FDA Can Require Sponsors to Develop and Implement REMS for *Prescription* Drug and Biological Products Approved under
 - New drug applications (NDAs)
 - Abbreviated NDAs (ANDAs), and
 - Biological license applications (BLAs)

REMS

Section 505-1 states that FDA may require a REMS:

- Before approval: If FDA determines a REMS is necessary to ensure that the benefits of the drug outweigh the risks
- Post approval: If FDA becomes aware of new safety information and determines a REMS is necessary to ensure the benefits of the drug outweigh the risks

Once notified by FDA that a REMS is necessary, the holder must submit a proposed REMS

REMS

- If an applicant believes a REMS would be necessary, applicants may also voluntarily submit a proposed REMS without having been required by FDA
 - With original application
 - In supplemental application
 - In an amendment to an existing original or supplemental application
- If an applicant voluntarily submits a proposed REMS, it will not be approved as a REMS unless and until the FDA determines that it is required to ensure that the benefits of the drug outweigh the risks and that it meets the FDAAA criteria

REMS and Generic Drugs

- Abbreviated New Drug Applications (ANDA) for generic drug products for which the reference listed drug has an approved RiskMAP will be approved with a comparable RiskMAP that includes the same essential elements.
- ANDAs for which the reference listed drug has a REMS will be approved with the elements of that REMS applicable to ANDAs.
 - ANDAs may only be required to have a Medication Guide and Elements to Assure Safe Use (ETASU) as elements of their REMS.

REMS are Enforceable

- Sponsor (applicant) may not introduce drug into interstate commerce if in violation of provisions.
- Drug may be found to be misbranded
- FDA can impose civil penalties for violations of the Act

Deemed REMS

- Section 909 stated that drugs approved before FDAAA with elements to assure safe use were deemed to have REMS
- On March 27, 2008, FDA published in the *Federal Register** a list of drugs that were identified as deemed to have an approved REMS, and directed holders of approved applications for those products to submit a proposed REMS by September 21, 2008.

*See *Federal Register* Notice "Identification of Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies (REMS) for Purposes of the Food and Drug Administration Amendments Act of 2007" (73 FR 16313, March 27, 2008)-

<http://www.fda.gov/OHRMS/DOCKETS/98fr/E8-6201.pdf>



Deemed REMS

- As of October 7, 2011, 10 Deemed REMS have been approved

Tracleer Letairis Thalomid Revlimid Lotronex	Isotretinoin Mifeprax Actiq Tikosyn Tysabri
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Factors that FDA must consider in determining the need for a REMS

- Size of the population likely to use the drug
- Seriousness of the disease
- Expected benefit of the drug
- Expected duration of treatment
- Seriousness of known or potential adverse events
- Whether the drug is a new molecular entity

REMS Elements

- Only required element is a timetable for submission of assessments of the REMS
- Sponsors submit evaluation of the effectiveness of the REMS
 - Required at minimum of 18 months, 3 years, 7 years after approval of the REMS (more frequently for REMS with ETASU)
 - REMS approval letter will include specifics of assessment plan
 - Negotiated during review of REMS
 - Generally, details of the methodology for assessment not included
 - Sponsor develops assessment methods
- FDA can require additional assessments
- FDA is requiring each REMS to have a goal against which it can be assessed



Other Elements of a REMS

- Medication Guides (if meets regulations in 21 CFR Part 208) and Patient Package Insert (PPI) (if insert may help mitigate serious risk of the drug)
- Communication plan if FDA determines plan may support implementation of an element of the REMS
- Elements to assure safe use
- Implementation system, if REMS includes certain elements to assure safe use

Medication Guides*

- FDA requires that Medication Guides be dispensed with certain prescribed drugs and biological products when the Agency determines that:
 - certain information is necessary to prevent serious adverse effects
 - patient decision-making should be informed by information about a known serious side effect with a product, or
 - patient adherence to directions for the use of a product are essential to its effectiveness
- Requirements for Medication Guides are found in the Title 21 of the Code of Federal Regulations Part 208 (21 CFR 208)

*Recent draft guidance explains that MGs will not be common element in a REMS, Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies



Medication Guides

- Medication Guides as Part of REMS
 - FDA may approve a MG under 21 CFR part 208 without requiring a REMS
 - When MG as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 208.1
 - May be few occasions when MG will be included in the REMS
- Medication Guides required as part of REMS are subject to the assessment and modification provisions under sections 505-1 (g) and (h) of the FD&C Act.
 - By eliminating the requirement for many Medication Guide only REMS, the number of patient surveys will decrease

Communication Plan

- FDA may determine that a communication plan targeted at health care providers is a necessary element of a REMS if it may support implementation of the REMS.
- May include:
 - sending letters to health care providers
 - disseminating information about REMS elements to encourage implementation by health care providers or to explain certain safety protocols, such as medical monitoring by periodic laboratory tests
 - disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use

Elements to Assure Safe Use (ETASU)

Requirements may include:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry



ETASU: Certification of Healthcare Providers

- A REMS may require health care providers who prescribe the drug to have particular training or experience, or to be specially certified
- Certifications may require, for example, that prescribers:
 - Are familiar with educational materials, risks of the drug, and conditions for safe use
 - Can diagnose and treat potential adverse reactions or are familiar with required monitoring



ETASU: Certification of Those Who Dispense

- A REMS may require pharmacies, practitioners, or health care settings that dispense the drug to be specially certified
- Certifications may require, for example, that dispensers:
 - Be familiar with educational materials, risks of the drug, and conditions for safe use
 - Agree to fill a prescription only after receiving prior authorization



ETASU: Dispense in Certain Healthcare Settings

- The REMS may require that the drug be dispensed to patients only in certain health care settings
 - for example, product can only be administered in hospitals or infusion centers



ETASU: Documentation of Safe-Use Conditions

- The REMS may require that the drug be dispensed to patients with evidence or other documentation of safe-use conditions
- Evidence of safe use conditions may include
 - Laboratory tests
 - Documentation of consent or counseling by patient
 - Patients receive the drug only after specified authorization is obtained (e.g., documented negative pregnancy test)

ETASU: Patient Monitoring

The REMS may require each patient using the drug be subject to certain monitoring

- Might require periodic blood tests or other monitoring at specified time periods
- Might require follow up questionnaire at specified time periods and after discontinuation of drug



ETASU: Registry

- The REMS may require each patient using the drug be enrolled in a registry
 - Provides information on patients prescribed the drug and allows follow-up on adverse events and trends

Implementation Systems

- REMS may include an implementation system related to ETASU in certification of pharmacies and hospitals, dispense only in certain healthcare settings, and safe use conditions.
- May require applicant to take reasonable steps to
 - monitor and evaluate implementation of such elements by health care providers, pharmacists, and other parties in the health care system who are responsible for implementing such elements; and
 - work to improve implementation of such elements by such persons.



FDAAA Numbers

March 25, 2008 – October 1, 2011

- New **REMS** approved for approximately 185 products
 - 124 Medication Guide only REMS (73 have since been released)
 - 61 REMS included more than a MG
 - 21 had elements to assure safe use and possibly other elements such as a communication plan or Medication Guide
 - 40 had a communication plan as the primary element and most also had a Medication Guide
- Published several draft and final FDAAA-related guidance documents
 - Draft guidance on Medication Guide Distribution and Inclusion in REMS
 - Draft guidance on Safety Related Labeling Changes
 - Final guidance on Postmarketing Studies and Clinical Trials
 - Draft guidance on REMS Content and Format

Recognizing Implementation Challenges

- Since REMS provisions took effect 3 years ago, we have heard concerns from stakeholders
- In July, 2010, FDA held a 2-day public meeting*
 - Over 60 individual presentations to obtain stakeholder views on the REMS program
 - Issues and Challenges associated with the development and implementation of REMS for drugs

* Risk Evaluation and Mitigation Strategy (REMS) Public Meeting,

<http://www.fda.gov/Drugs/NewsEvents/ucm210201.htm>

What We heard at Public Meeting

- REMS are necessary to preserve access to drugs whose risks would otherwise exceed benefits
- Multiplicity of unique REMS places burdens on the healthcare system
 - Particularly, REMS with elements to assure safe use
 - Also, “Medication Guide-only” REMS
- Standardized REMS programs would reduce burden on the healthcare system

What We heard at Public Meeting

- Consult with prescribers, pharmacists, patient groups, and others to get input
 - How to design REMS so that they preserve access while effectively addressing risk
- Integrate REMS into existing healthcare systems to reduce burden
- Use developing informatics systems (e.g., e- prescribing, e-health record) to implement REMS more efficiently and effectively

Next Steps for REMS

- Developing a framework for improving REMS
- Will be engaging in public outreach through a variety of different efforts to discuss various components of the framework
- Objective: develop standardized REMS that can be plugged into existing healthcare systems to address particular risks and categories of risk

Resources

Approved Risk Evaluation and Mitigation Strategies (REMS)

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm>

Postmarket Drug Safety Information for Patients and Providers

<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>

Medication Guides

<http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm>

Questions and Answers on Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)

<http://www.fda.gov/Drugs/DrugSafety/ucm248459.htm>

Resources

Information by Drug Class

<http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/default.htm>

Drug Safety Communications

<http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>

MedWatch: The FDA Safety Information and Adverse Event Reporting Program

<http://www.fda.gov/Safety/MedWatch/default.htm>

Drug Safety Labeling Changes

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm>



Questions??

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